work with others in the health field to help shape the changes which are sure to occur down the road. One looks to our leadership to see to it that we get our act together in timely fashion.

—MSMW

The Evaluation of Thromboembolic Diseases

What to Do Now That the Radioimmunoassay Has Arrived

ABOUT A DECADE AGO, an article entitled "The Diagnosis of Hyperparathyroidism (or What to Do until the Immunoassay Comes)" appeared in a leading clinical journal.[1] Bolstered by success with other radioimmunoassays, endocrinologists confidently predicted that a similar assay for parathyroid hormone would greatly simplify the diagnosis of hypercalcemia. We now know that this prediction did not prove entirely true and that considerable clinical acumen and extensive laboratory testing are still necessary to establish the correct diagnosis in a hypercalcemic patient. As we enter the second year of a new decade, radioimmunoassays are being developed for the study of patients with thromboembolic disorders and are predicted to have equal use.

Although thromboembolism occurs in a variety of clinical settings, it is facilitated by biochemical or cellular defects which permit activated products of coagulation to remain in the circulation, inducing a "hypercoagulable" state. Congenital absence of antithrombin, a plasma protein which inactivates serine proteases in the coagulation cascade, is a well-defined biochemical abnormality which is associated with a high incidence of thromboembolism. Undoubtedly, there are many other inherited and acquired abnormalities that create this hypercoagulable state, thereby predisposing patients to thromboembolism. For example, women who use oral contraceptives have a higher than expected incidence of thrombosis and vascular disease. It is clear that conventional coagulation tests, which are designed to measure failure of hemostasis and bleeding, are not able to predict thrombosis. Thus, a new generation of more appropriate tests has been developed to measure the events in blood coagulation that precede or accompany thrombus formation.[2] It is timely to review the limitations of these tests and to determine if they can detect patients with coagulation abnormalities before the onset of clinical thrombotic events.

ABBREVIATIONS USED IN TEXT

FPA = fibrinopeptide A
PF4 = platelet factor 4
βTG = β-thromboglobulin

A pioneering example of such a test is an immunoassay for fibrinopeptide A (FPA), one of two small peptides cleaved by thrombin during the conversion of fibrinogen to fibrin. FPA levels are elevated in patients with deep venous thrombosis and pulmonary embolism, but return to normal following administration of heparin.[3] Although FPA levels are clearly elevated in patients who have overt thrombosis, they have not yet been measured in such patients before thrombotic episodes. In addition, FPA levels are also elevated in patients with nonthrombotic inflammatory or autoimmune disorders such as systemic lupus erythematosus.

There are some technical problems which have limited the use of this assay. First, the available antisera cross-react extensively with intact fibrinogen so that all residual fibrinogen must be removed from test plasma before doing the assay. To be certain that the measured FPA levels reflect thrombin's action on fibrinogen, another immunoassay for a plasmin-generated fibrin fragment, such as fragment 1-42 of the β-chain of fibrinogen, must be done simultaneously.

More recently, assays have been developed for prothrombin-activation peptides and for the thrombin-antithrombin complexes that form in plasma after thrombin generation.[4] These assays do not require plasma processing because they use a highly purified antibody which recognizes new antigenic determinants on the protein fragment or complex, even in the presence of an excess of precursor molecules. These newer assays are promising but have not yet been tested in clinical situations.

Elsewhere in this issue, Wohl reviews the use of secreted platelet proteins to study thromboembolism and vascular disease. Plasma levels of two of these proteins, platelet factor 4 (PF4) and β-thromboglobulin (βTG), are elevated in a number of clinical situations. First, they are slightly higher than normal in patients with chronic vascular disease or diabetes mellitus, although there is considerable overlap within the

normal range. In addition, plasma levels of the two proteins are more strikingly elevated in patients with deep venous thrombosis, pulmonary embolism, arterial occlusion and myocardial infarction. Finally, PF4 and βTG are elevated in patients during episodes of spontaneous and exercise-induced myocardial ischemia and angina pectoris. Thus, an increased plasma level can signify platelet activation in chronic vascular disease or in acute ischemia and thrombosis. Although there is a close correlation, the tests do not distinguish between a primary and secondary platelet role in these diseases.

There are also some serious technical limitations to these assays. For example, it is not yet clear which of the protein measurements provides the best estimate of in vivo platelet activation. Because βTG is cleared and metabolized by the kidney, renal failure increases the plasma level of βTG without any activation of the coagulation system. PF4 might seem to be a superior marker because its plasma level is not influenced by renal function. However, it adheres to endothelial cells lining blood vessels and can be displaced by the administration of therapeutic concentrations of heparin.[5] While the presence of PF4 on vascular endothelium may have biological importance and may, in fact, modulate coagulation reactions, this interaction complicates the interpretation of plasma radioimmunoassays. To circumvent these problems, some investigators have suggested that both PF4 and βTG should be measured simultaneously and that a high ratio of βTG to PF4 would reflect in vivo release, whereas a ratio that approximates their content in platelets might represent release in vitro. Interestingly, in most clinical reports, plasma levels of both proteins rise in parallel.

Given these uncertainties, can such tests be applied clinically? If clinical application means ordering a battery of radioimmunoassays to diagnose early vascular disease or to predict impending thrombosis, the answer is probably no. However, techniques that can measure secreted platelet proteins and activation products or complexes formed during the coagulation process are valuable tools for clinical investigation. The assays should permit studies with human subjects that have previously been possible only with purified protein mixtures in vitro. For example, it should now be possible to determine (1) if coagulation reactions proceed in vivo by the pathways postulated from experiments in test tubes, (2) if there are patients in whom there is evidence for activation of coagulation before clinical thromboembolism (hypercoagulable state), (3) if the tests change in a predictable manner during acute thrombotic events and (4) if they can be used to monitor the efficacy of antithrombotic therapy.

It is hoped that the answers to these questions, as well as many other unforeseen ones, will soon become available. It may then be possible for clinicians to identify patients with a predisposition to thrombosis and then prescribe appropriate therapy. Radioimmunoassays of the coagulation system could then become as useful as their endocrine counterparts. However, only with more knowledge of the progression of such illnesses and the effect of therapy, both on the clinical outcome and the laboratory tests, will it be possible to predict the usefulness of these tests. For practicing physicians, the best approach, for the moment, may be to watch and wait. It should be remembered that, in medicine as in other human endeavors, "Time cools, time clarifies. . . ."[6]

ROBERT I. HANDIN, MD
Hemostasis Unit
Brigham and Women's Hospitals
Department of Medicine
Harvard Medical School
Boston

REFERENCES

1. Raisz LG: The diagnosis of hyperparathyroidism (or what to do until the immunoassay comes). N Engl J Med 285:1006-1010, Oct 28, 1971

2. Hirsh J: Blood tests for the diagnosis of venous and arterial thrombosis. Blood 57:1-8, Jan 1981

3. Nossel HL, Yudelman I, Canfield R, et al: Measurement of fibrinopeptide A in human blood. J Clin Invest 54:43-48, Jul 1974

4. Rosenberg RD: Hypercoagulability and methods for monitoring anticoagulant therapy, *In* Frantantoni J, Wessler S (Eds): Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism, DHEW Pub No. NIH 78-866. US Dept of Health, Education, and Welfare, National Institutes of Health, 1978, pp 28-42

5. Busch C, Dawes J, Pepper D, et al: Binding of platelet factor 4 to cultured human umbilical vein endothelial cells. Thromb Res 19:129-137, Jul-Aug 1980

6. Mann T: The Magic Mountain. New York, Alfred E. Knopf, 1927

Adoption and Freedom of Information

ELSEWHERE IN THIS ISSUE Davis and Brown discuss changing attitudes and circumstances with respect to adoptions. Of particular interest is the fairly recent trend toward what might be called freedom of information among what is called the "adoption triangle"—that is, the true parents, the adopted child and the adoptive parents. A case is made that, for all concerned, knowing is better than not knowing and that physicians should do what they can to facilitate the exchange of information, whether in the care of their patients or by